which it is most nearly connected, to make and/or use the invention." The Office has discussed the *Wands* factors and cited papers by Clark and Li et al. in support of the rejection.

Applicant respectfully traverses this ground of rejection. Because the Office has analyzed the claims in terms of the individual Wands factors, each of these factors will be addressed individually. However, Applicant wishes to note that it is improper to conclude that a disclosure is not enabling based on an analysis of only one of these factors while ignoring one or more of the others. Any conclusion of non-enablement must be based on the evidence as a whole. MPEP 2164.01(a).

The Nature of the Invention

Applicant agrees that the present claims are drawn to methods of reducing cell proliferation or extracellular matrix production (claims 1-6, 9, and 22-23), methods of treating fibrosis (claims 11-13, 15, and 24-25), and methods of reducing stellate cell activation (claims 17-21). The claims encompass, in general, antibody therapy. The claims also encompass antibody therapy for treatment of fibrosis, but not all claims are so limited. The Office has rejected the claims as a group, and has not addressed the patentability of individual claims or groups of claims. Applicant submits that the claims do not stand or fall together.

The Breadth of the Claims

Applicant has presented claims of varying scope. Claim 1 is directed to a method of reducing cell proliferation or extracellular matrix production in a mammal using a zvegf3 antagonist antibody that specifically binds to a defined dimeric protein. Claim 2 is directed to a method of reducing proliferation of certain cell types. Claim 3 recites that extracellular matrix production is reduced. Claims 4-6 recite fibroprolferative disorders of specific tissues. Claims 9, 22, and 23 further define the antibody. Claim 11 is directed to a method of treating fibrosis using the antibody recited in claim 1. Claims 12 and 13 recite that the fibrosis is liver fibrosis or kidney fibrosis, respectively. Claims 15, 24, and 25 further define the antibody. Claim 17 is directed to a method of reducing stellate cell activation in a mammal using the antibody recited in claims 1 and 11. Claim 18 recites that the stellate cells are liver stellate cells. Claims 19-21 further define the antibody.

The Office has characterized the claims as "very broad" and as encompassing "reducing proliferation and extracellular matrix production of any type of cell and treating any type of fibrosis", and "humanized or non-humanized" "monoclonal or polyclonal" antibodies. The Office has, however, failed to differentiate among the 20 pending claims and their varying scopes, and has instead applied the same broad-brush rejection to all claims, apparently disregarding recited limitations.

The Unpredictability of the Art and the State of the Prior Art

a) The Clark Disclosure

The Office has asserted, citing Clark, that "the relevant art considered antibody therapy to be unpredictable." Clark has been relied upon as teaching that the antiglobulin response is perceived as a major problem in the clinical development of therapeutic antibodies and, thus, "antibody therapy is an unpredictable art."

Applicant respectfully submits that the antibody therapy art is not nearly so unpredictable as the Office contends. The use of therapeutic antibodies, including antibodies to growth factors and their receptors, is well known in the art. A number of therapeutic antibodies are currently on the market (and have been since before Applicant's effective filing date) or in clinical trials. Genentech's HERCEPTIN® (Trastuzumab) is an antibody that binds to a "growth factor-like receptor" on the cell surface. HERCEPTIN® was approved for marketing by the FDA in September 1998 (see enclosed product information). Centocor Inc's REMICADE® (Infliximab) is an antibody that "neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors" (REMICADE® package insert, copy enclosed). TNFα is a growth factor (Sporn and Roberts, *Nature* 332:217-219, 1988; copy enclosed). REMICADE® was approved for marketing by the FDA in August 1998 (Centocor Inc. Form 10K for the fiscal year ended December 31, 1998, page 3; copy enclosed). Amgen and Abgenix are currently developing ABX-EGF, a fully human monoclonal antibody directed against epidermal growth factor receptors. The product is currently in Phase 2 clinical trials (Amgen Product Pipeline, http://www.amgen.com/product/pipeline.html#abx-egf, pp. 2, 7; copy enclosed). REOPRO® (abciximab) is an anti-integrin monoclonal antibody that binds to the glycoprotein IIb/IIIa (GP IIb/IIIa) receptor on the surface of platelets, thereby preventing platelets from sticking together and forming a clot. It also binds to the vitronectin and MAC-1 receptors, which play a role in smooth muscle proliferation and inflammation, respectively. REOPRO® was cleared for marketing in the U.S. and Europe in December 1994 (Centocor, Inc., http://www.centocor.com/cgi-bin/site/products/prod_reopro.cgi, 2002; copy enclosed).

With regard to the therapeutic use of antibodies in general, Moran (*BioWorld Today*, June 13, 2002, page 6; copy enclosed) discloses that 11 therapeutic antibodies are on the market and over 350 are at different stages of clinical development. Sales were $2-3 billion in 2001, and are projected to increase to $20 billion in 2002. MedImmune's SYNAGIS® (palivizumab) had "sales of $516 million in the 2000-2001 disease season." This product was in general use in the United States in 1998-1999 (MedImmune Press Release, Nov. 4, 1999; copy enclosed).

A report by Reuters ("Monoclonal antibody drug sales soaring—report." Reuters Company News, October 1, 2002; copy enclosed) states, "Sales of monoclonal antibody drugs soared by 57 percent to $2.9 billion in 2001 and could total as much as $12.1 billion by 2010." Genentech's Rituxan and Johnson & Johnson's Remicade are reported as being the best-selling monoclonal antibody and the best seller outside the cancer field, respectively, each with projected billion dollar plus sales. RITUXAN® (Rituximab), an antibody to the CD20 antigen on the surface of normal and malignant B cells, was approved by the U.S. Food and Drug Administration (FDA) in November 1997 (Genentech, Inc. Product Information, http://www.genentech.com/gene/products/information/oncology/rituxan/index.jsp, 2002; copy enclosed). As discussed *supra*, REMICADE® has been marketed since 1998.

Antibodies have been successfully tested in clinical applications related to those addressed by Applicant's invention. For example, CAT-152 is an anti-TGF-β monoclonal antibody under development by Cambridge Antibody Technology (CAT). A September 6, 1999 CAT press release (copy enclosed) discloses data on a Phase I/IIa trial of CAT-152 in post-operative scarring in glaucoma surgery:

> "CAT-152 was shown to be safe and well tolerated in this group of patients: there were no serious local injection site reactions and no drug-related serious adverse events were reported." [Emphasis added.]

It is clear from the CAT-152 study and other examples cited herein that therapeutic antibodies can be used in humans without untoward side effects.

Glennie and Johnson, *Immunol. Today* 21:403-410, 2000 (cited by Clark; copy enclosed) disclose at page 403:

> In the past five years, however, the situation has changed dramatically, with numerous mAbs now showing clinical potential, and a further seven approved for human treatment. Furthermore, all indications are that this upward trend will continue, with a quarter of all new biological products currently undergoing clinical development being antibody based.

Table I of Glennie and Johnson discloses a "selection"of antibodies in clinical trials or on the market. The table includes ten antibodies that had been approved by the FDA or foreign regulatory authorities.

While Clark may have "perceived" the antiglobulin response to have been "a major problem in the clinical development of thereapeutic antibodies" (Clark at page 397), the evidence cited above clearly demonstrates that whatever problems may have actually existed were hardly insurmountable. Indeed, the number of antibodies on the market and in the clinic by 2000 shows that clinical develoment of antibodies was within the level of ordinary skill in the art.

Clark's perceived problems relate to factors that the Office has not shown to bear on Applicant's claimed invention. Much of the Clark article deals with the human anti-mouse immune response (HAMA) and human anti-human antibody responses (HAHA). Clark discloses, however, that such responses merely "cut short the therapeutic window" (page 397, right column). Glennie and Johnson disclose that a HAMA response "might actually improve the outcome" of antibody therapy (page 403, right column) and, in any event, "mAbs are achieving the goal of 'a long-term effect following a short-term treatment'" (page 406, right column). Other issues discussed by Clark, including royalties and production costs (pages 399-401), are purely business considerations that have no bearing on patentability. The sweeping generalization presented in the abstract of the Clark article is circumscribed by his "Concluding remarks" on page 401:

> However, the anti-idiotype response is generally only a problem where repeated treatments are required for chronic and relapsing diseases such as in therapy of autoimmune disease. Indeed for many therapeutic applications in acute disease situations, the possibility of an anti-idiotype response is not likely to have a major impact on their efficacy in the vast majority of patients. [Emphasis added; citations omitted.]

Even if, *arguendo*, Applicant's claimed methods resulted in immunogenic reactions in some patients, the Office has not presented evidence that such reactions would negate the therapeutic efficacy of those methods. Immunogenic complications have not prevented the use of therapeutic antiodies now on the market. In a trial of SYNAGIS®, "the incidence of anti-humanized antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis® group" (SYNAGIS® package insert, 1999; copy enclosed). Transient, low titer reactivity was also seen in one of fifty-six patients receiving the antibody for a second season (*id.*). In clinical trials, SYNAGIS® was administered in five montly injections (*id.*). In studies with RITUXAN®, 4 of 356 patients had a detectable human anti-chimeric antibody response (RITUXAN® package insert, page 1, right column, 2002; copy enclosed). The Office has not provided evidence that an anti-idiotype response would render inoperable Applicant's claimed methods of reducing cell proliferation or extracellular matrix production (claims 1-6, 9, and 22-23), methods of treating fibrosis (claims 11-13, 15 and 24-25), or methods of reducing stellate cell activation (claims 17-21).

b) The Li et al. Disclosure

The Office has cited Li et al. as disclosing, "The ideal drug would be one which is easily delivered and well tolerated, with high liver specificity and few adverse effects" (emphasis added). The Office has also relied on Li et al. to support the assertion that

"there was no guarantee that the untested therapies that were proposed would actually develop into a reliable therapy" and that "several key questions need to be answered."

Applicant respectfully submits that "ideal" is not the standard for patentability under Section 112. As to there being "no guarantee that the untested therapies . . . would actually develop . . ." (Off. Act. at p. 5), it is respectfully submitted that patentability is not predicated on a "guarantee" of a reliable therapy. See, MPEP 2107.03 ("The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted." [Emphasis added.]). All that is required is a reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). Furthermore, issues of full safety (i.e., "adverse effects") and effectiveness of therapeutic methods are the province of the Food and Drug Administration, not the Patent and Trademark Office. *Scott v. Finney*, 34 F.3d 1058, 32 USPQ2d 1115 (Fed. Cir. 1994). Even assuming, *arguendo*, that "key questions need to be answered" in order to develop an "ideal drug," Li et al. clearly disclose that therapeutic strategies for liver injury currently exist (pages 623-624).

Finally, the Office has asserted that "it also has not been determined if the activated stellate cells can be reverted to a quiescent state." Applicant respectfully submits that this assertion has been made outside the context of the source article. As disclosed by Li et al. at page 622, right column:

> The fate of activated stellate cells as liver injury resolves is under scrutiny. It is not established whether activated stellate cells can revert to a quiescent phenotype or must be selectively cleared by apoptosis in this setting. However, there is now increasing evidence of a role for apoptosis in stellate cell clearance. [Emphasis added.]

Despite a lack of understanding of the process, liver injury can resolve and stellate cells can be cleared. See also, Iredale et al., *J. Clin. Invest.* 3:538-549, 1998 (copy enclosed), who studied a rat model of spontaneous resolution of liver fibrosis and concluded that stellate cell apoptosis is "central to the diminution of activated HSC numbers during recovery" (page 548, left column).

Also in regard to the reversion of activated stellate cells to the quiescent state, Applicant initially notes that only claims 17-21 recite a method of reducing stellate cell activation. "Reducing stellate cell activation," however, does not require that activated stellate cells revert to the quiescent state. As discussed *supra*, activated stellate cells can be

cleared by apoptosis. Furthermore, a population of stellate cells would not be expected to be activated as a whole. Rather, the process is a ongoing one. See, Friedman (*Seminars in Liver Disease* 19:129-140, 1999; cited by Applicant as reference A23 in the Information Disclosure Statement filed May 14, 2002) at page 132, right column:

> Not all stellate cells activate synchronously after liver injury. Rather, with continued injury an increasing percentage of cells is recruited . . . Extraordinary progress has occurred in the elucidation of mechanisms underlying stellate cell activation, and particularly in the critical role played by cytokines.

Hence, stellate cell activation can be reduced by interfering with the underlying mechanism, such as by targeting relevant cytokines.

The art has recognized, and continues to recognize, that intervention in the process of stellate cell activation is among the most promising approaches to treatment of liver fibrosis. According to Friedman (*ibid.*):

> Identifying key roles for cytokines in hepatic fibrosis will lead to new therapies for hepatic fibrosis . . . the general strategy will be to neutralize those cytokines which stimulate features of activated stellate cells or augment those which restrain it. (*Id.*, at p. 136, left column.)

Among the approaches that Friedman discloses for treating hepatic fibrosis are inhibiting the production or activation of cytokines, including TGF-β1; using antibodies to cytokines; and downregulating stellate cell activation. Li et al. includes a similar teaching at page 625, right column:

> "Hepatic growth factor inhibits liver fibrosis and promotes liver regeneration in animal models of liver injury. A deletion variant of HGF is effective in inhibiting stellate cell activation, down-regulating the mRNA expression of pro-collagens and TGFβ1 and stimulating liver regeneration."

Albanis and Friedman (*Clinics in Liver Disease* 5:315-334, 2001; copy enclosed; cited as disclosing scientific principles) disclose at pages 320-324 that hepatic stellate cell activation is a two-stage process, involving both initiation and perpetuation. See also Friedman (*ibid.*) at pages 132-136. Changes characteristic of the perpetuation phase include proliferation due to the action of mitogenic factors; increased extracellular matrix production, which results from increased TGF-β1 production by stellate cells; release of cytokines, including TGF-β1; matrix degradation; and chemotaxis. According to Friedman (*ibid.*), TGF-β1 is upregulated in activated stellate cells, autocrine expression is among the most important sources of this cytokine in hepatic fibrosis, and TGF-β1 is important for extracellular matrix remodelling (page 135). Thus, the art clearly recognizes that stellate cell activation is a process that is amenable to therapeutic intervention.

Furthermore, the record shows that intervention with relevant cytokine antagonists would be expected to reduce fibrosis. See, for example, Li et al. at page 623, left column ("In the future, targeting of stellate cells and fibrogenic mediators will be a mainstay of therapy."). Such "targeting" is within the scope of Applicant's claimed invention. Applicant has shown that zvegf3 stimulates TGF-β1 production by hepatic stellate cells (p. 40), that zvegf3 overexpression promotes proliferation of stellate cells and/or fibroblasts in liver (pp. 39-40), and that zvegf3 is mitogenic for stellate cells (pp. 36-37) and mesangial cells (pp. 40-41) (which play a role in renal injury that parallels that of stellate cells in hepatic injury as disclosed by Friedman at page 132, right column). These activities are closely correlated with key events in stellate cell activation, liver fibrosis, and kidney fibrosis. Hence, zvegf3 is indicated to be relevant to fibrosis (including liver and kidney fibrosis), and one skilled in the art would therefore reasonably predict that the claimed methods would be useful.

In view of the disclosures discussed *supra*, it is evident that reversion of stellate cells to a quiescent state (assuming, *arguendo*, that such reversion is problematic) is not required for reducing stellate cell activation, nor is it a necessary component of reducing cell proliferation as recited in claims 1-6, 9, and 22-23; or of treating fibrosis as recited in claims 11-13, 15, and 24-25.

c) The State of the Art

The state of the art of antibody therapy has been discussed *supra*. Applicant submits that the evidence shows that therapeutic antibodies are an established treatment modality warranting substantial investment by the pharmaceutical industry.

The state of the art of treatment of fibrosis was much more advanced than the Office seems to imply in the Office Action. Li et al. disclose existing therapies for liver fibrosis, including removing injurious stimuli and suppressing inflammation using, for example, corticosteroids. Other agents, such as colchicine, have also been used in humans or in animal models. The association of PDGF with fibrotic conditions is also known in the art as shown by references of record. See, for example, Clader et al., U.S. Patent No. 5,238,950; Brady et al., *Biochem. Biophys. Res. Comm.* 248:174-179, 1998; and Johnson et al., *J. Exp. Med.* 175:1413-1416, 1992, copies of which were provided with Applicant's Information Disclosure Statement of May 14, 2002.

Working Examples and Guidance in the Specification

According to the Office, "The specification has no working examples, whatsoever, demonstrating administration of the zvegf3 antibodies to a mammal."

Applicant respectfully submits that compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph does not turn on whether an example is disclosed. See, MPEP 2164.02. The absence of working examples will not by itself render the invention non-enabled. *Id.*

Applicant's specification includes working examples using *in vitro* models, which the Office has not acknowledged. Thus, the Office has not met its initial burden in establishing a *prima facie* case of unpatentability:

> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigourous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985." MPEP 2164.02.

Thus, an *in vitro* model that correlates with the claimed methods constitutes a working example.

Claims 1-6, 9, 22, and 23 are directed to a method of reducing cell proliferation or extracellular matrix production. Applicant has disclosed experimental results demonstrating that zvegf3 growth factor domain protein is mitogenic for cells expressing cell-surface PDGF α-receptor subunit (specification at page 4) and, in particular, for mesangial cells (pp. 40-41), stellate cells (pp. 36-37), and osteoblasts (p. 38). In view of Applicant's disclosure, one of ordinary skill in the art would expect the zvegf3 growth factor domain to be mitogenic for other cells that express the PDGF α-receptor subunit, such as endothelial cells, smooth muscle cells, fibroblasts, osteoclasts, and interstitial cells. See, for example, Heldin and Westermark, *Physiological Reviews* 79:1283, 1288, 1999 (cited as reference A26 in Applicant's Information Disclosure Statement of May 14, 2002). Based on Applicant' disclosure, one of ordinary skill in the art would reasonably conclude that if zvegf3 is mitogenic for these cells, then an antibody that inhibits zvegf3 biological activity would be useful in reducing proliferation of these cells. Applicant has further shown, in Example 13, that the zvegf3 growth factor domain protein stimulates TGF-β1 production by hepatic stellate cells. TGF-β1 is known to be profibrogenic (Li et al. at page 620, right column) and is upregulated in activated stellate cells (Friedman, *ibid.*, page 135, left column). Activated stellate cells are the primary source of extracellular matrix in hepatic fibrosis (Friedman at page 129, left column), and TGF-β1 is important in extracellular matrix remodelling (Friedman at page 135). Based on Applicant's disclosure, one of ordinary skill in the art would reasonably conclude that an antibody that inhibits zvegf3 biological activity would be useful in reducing extracellular matrix production.

Claims 11, 12, 13, 15, and 23-25 are directed to a method of treating fibrosis in a mammal using a zvegf3 antagonist antibody that specifically binds to a defined dimeric protein. Claim 12 recites that the fibrosis is liver fibrosis. Applicant has shown a correlation between zvegf3 overexpression and liver fibrosis in an animal model (specification at pages 39-40). Mice infected with a zvegf3-encoding adenoviral vector had visibly enlarged livers with proliferation of stellate cells and/or fibroblasts. As discussed *supra*, proliferation is an indicator of hepatic stellate cell activation. Upon activation, hepatic stellate cells transform to a myofibroblast-like phenotype as disclosed by Iredale et al. (*ibid.*) at page 538, right column. In addition, Applicant has shown at page 40 that the zvegf3 growth factor domain protein stimulates TGF-β production by stellate cells. Upregulation of TGF-β is a marker of stellate cell activation and a key component of hepatic fibrosis as disclosed by Li et al. and by Friedman. See also, Albanis and Friedman, *ibid.*, at page 322 ("Because of its importance in fibrogenesis, neutralizing TGF-β activity is a major strategy for treating hepatic fibrosis, as discussed later."). Claim 13 recites that the fibrosis is kidney fibrosis. As disclosed at page 40 of Applicant's specification, animals overexpressing zvegf3 showed increased cell proliferation in kidney. There is thus a reasonable correlation between Applicant's disclosure and claims 11, 12, 13, 15, and 23-25.

Claims 17-21 are directed to a method of reducing stellate cell activation in a mammal. As discussed above, Applicant has disclosed experimental results showing that zvegf3 proteins promote stellate cell proliferation and upregulation of TGF-β production by stellate cells. Proliferation and TGF-β upregulation are markers of stellate cell activation (e.g., Li et al. at page 620, left column and page 622, left column). On the basis of the disclosed results, one of ordinary skill in the art would reasonably conclude that the recited antibodies would be useful in reducing stellate cell activation in a mammal.

With regard to statements at page 6 of the Office Action that "[t]here is no evidence provided that the antibodies are not immunogenic, and do not activate the host cells immune response to the therapeutic agent," Applicant respectfully submits that safety of therapeutic agents is not within the purview of the Patent and Trademark Office. See, MPEP 2164.05:

> However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled. See *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].")

See also, MPEP 2164.01(c) ("the applicant need not demonstrate that the invention is completely safe."). For reasons discussed above, Applicant further submits that the art, taken

as a whole, does not support the Office's contention that antibody therapy is unpredictable due to antiglobulin responses. Applicant notes that the only document of record supporting the Office's contention of antiglobulin responses is Clark, whereas Applicant has now submitted numerous publications showing that such responses, even when they occur, do not preclude therapeutic use.

Formulation and administration of antibodies are disclosed in Applicants' specification at pages 17-18. This disclosure includes guidance on formulation, routes of administration, and dose. Therapeutic use of antibodies is well known in the art as demonstrated by the antibodies that are currently on the market and in clinical trials. In view of the high level of skill in the art and the routine performance of complex testing in the pharmaceutical arts, Applicant's disclosure is believed to provide guidance commensurate with the claims and the statutory requirements. "If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." MPEP 2164.01(c).

Tests, including animal tests, that can be used in quantitating the activities of particular antibodies are disclosed at pages 19-20.

Quantity of Experimentation

According to the Office, the "quantity of experimentation in this area is extremely large" and would include creation of the claimed antibodies, demonstration of the desired effects (including in animal models), and testing in human subjects. The Office further believes that the experimentation "would require years of inventive effort" and would have to demonstrate "that the antibodies are tolerated by the patients." Office Action at pages 6-7.

A rejection cannot be based solely on the quantity of experimentation needed to make or use the invention. See, MPEP 2164.01(a) ("It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole.").

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. MPEP 2164.01. In the pharmaceutical arts, complex experimentation is, without question, the norm.

With regard to testing in humans, Applicant again submits that complete testing for safety and efficacy in humans is the province of Food and Drug Administration, not

the Patent and Trademark Office. Data from human trials are not required to show patentability. See, MPEP 2107.03.IV:

> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders, even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims. [Citations omitted.]

Serious side effects do not necessarily negate the use of a drug. See, for example, the enclosed RITUXAN® and REOPRO® product information.

Applicant has disclosed both *in vitro* and *in vivo* data, and has shown that these data have a reasonable correlation with the claimed invention, including methods of reducing cell proliferation or extracellular matrix production (claims 1-6, 9, and 22-23), methods of treating fibrosis (claims 11-13, 15 and 24-25), and methods of reducing stellate cell activation (claims 17-21). No undue experimentation is believed to be required to practice the claimed invention.

Level of Skill in the Art

Applicant agrees with the Office that the level of skill in the art is high. Thus, the ordinarily skilled artisan is equipped with extensive tools and training with which to implement and adapt Applicant's teachings toward practicing the full scope of the claimed invention. Applicant's teachings provide detailed instructions and guidance for skilled workers to achieve these goals, whereas the Office has provided no concrete evidence to show that it would be impracticable, or would require ingenuity beyond the level of the ordinary artisan, to do so.

Applicant believes that each rejection has been addressed and overcome. Reconsideration of the application and its allowance are requested. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6673.

Respectfully Submitted,

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